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Chiral Vinylphosphonate and Phosphonate Analogues of the Immunosuppressive Agent FTY720

Xuequan Lu,[†] Chaode Sun,[†] William J. Valentine,[‡] Shuyu E,[‡] Jianxiong Liu,[‡] Gabor Tigyi,[‡] and Robert Bittman[†,*]

Department of Chemistry and Biochemistry, Queens College of The City University of New York, Flushing, New York 11367-1597, and Department of Physiology, University of Tennessee Health Science Center, Memphis, Tennessee 38163

robert.bittman@qc.cuny.edu

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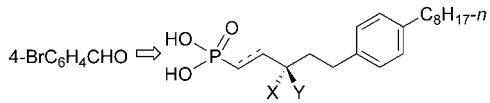

(*S*)-4, (*S*)-5: X = NH_2, Y = CH_2OH Both have anti-apoptotic activity; (*S*)-**5** is not a $S1P_1$ agonist

(*R*)-4, (*R*)-5: X = CH_2OH, Y = NH_2 Both lack anti-apoptotic activity but are $S1P_1$ agonists

The first enantioselective synthesis of chiral isosteric phosphonate analogues of FTY720 is described. One of these analogues, FTY720-(*E*)-vinylphosphonate (*S*)-**5**, but not its *R* enantiomer, elicited a potent antiapoptotic effect in intestinal epithelial cells, suggesting that it exerts its action via the enantioselective activation of a receptor. (*S*)-**5** failed to activate the sphingosine 1-phosphate type 1 ($S1P_1$) receptor.

FTY720 (2-amino-[2-(4-*n*-octylphenyl)ethyl]-1,3-propanediol, Fingolimod, **1**, Chart 1) is a synthetic analogue of the chiral sphingolipid myriocin (**2**).[1] As an analogue of sphingosine, FTY720 is phosphorylated in vivo by sphingosine kinases, affording (*S*)-FTY720-phosphate (**3**), which activates four of the five known sphingosine 1-phosphate (S1P, **2a**) G protein-coupled receptors.[2]

Internalization and subsequent polyubiquitination of the S1P receptors leads to their proteasomal degradation and renders the cells unresponsive to S1P; therefore, lymphocytes are not capable of recirculation to peripheral inflammatory tissues.[3] Thus, FTY720 has therapeutic potential and, in fact, is the first S1P receptor modulator that has entered the stage of a phase-III clinical study.[4]

Several syntheses of **1**[5] and of phosphate **3** have been accomplished.[6] In contrast to phosphates such as **3**, phosphonate analogues are resistant to the action of lipid phosphate phosphatases and may offer improved cellular stability. A racemic mixture of the nonhydrolyzable phosphonate analogue of FTY720 (**4**) was reported in which the C−O−P bond is replaced with a C−C−P bond;[2b] *rac*-**4** was found to be a high-affinity agonist of the S1P-type 1 receptor ($S1P_1$), with a similar potency as (*S*)-**3**.[7] We report here the first asymmetric syntheses of the chiral phosphonate analogues of FTY720, (*R*)-**4** and (*S*)-**4**. Oxazoline intermediate (*S*)-**14** (Scheme 1), prepared by a modification of our previous route,[6c] was further elaborated to give the corresponding (*E*)-vinylphosphonate analogue (*S*)-**5**. We have included a preliminary pharmacological characterization of the effects of these analogues on the nontransformed rat intestinal epithelial cell line IEC-6. This study revealed that (*S*)-**5**, but not its (*R*) enantiomer, exerts a potent antiapoptotic effect in a camptothecin (CPT)-induced apoptosis model.[8] Unlike phosphate (*S*)-**3**, (*S*)-**5** did not activate the $S1P_1$ receptor of the Endothelial Differentiation Gene (EDG) family of G protein-coupled receptors, making it a novel enantioselective probe activating a cytoprotective mechanism against apoptosis induced by DNA damage.

Wittig reaction of 4-bromobenzaldehyde with the ylide of *n*-heptyltriphenylphosphonium bromide gave arylalkene **6** as an *E,Z* (1:3) mixture (Scheme 1). Sonogashira coupling between **6** and 4-(phenylmethoxy)-1-butyne delivered enyne **7** as a 1:3 *E*:*Z* mixture in 92% yield. Alcohol **8** was obtained on reduction of the unsaturated bonds and hydrogenolysis of the *O*-benzyl group in the presence of Pearlman's catalyst. After Swern oxidation of **8** provided aldehyde **9**, use of a Mannich reagent,

[†] CUNY.

[‡] University of Tennessee Health Science Center.

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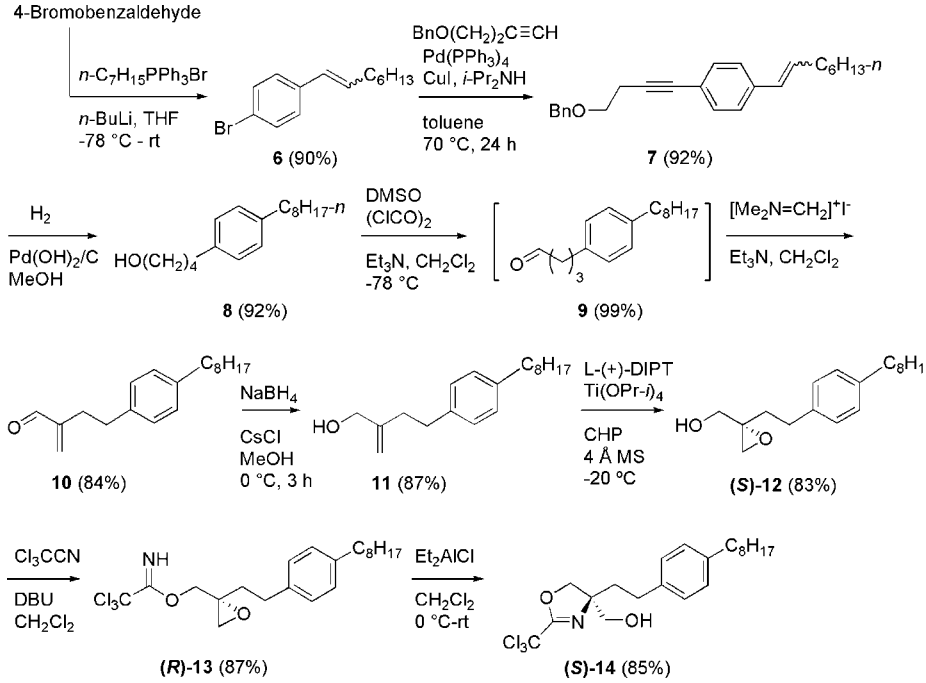
SCHEME 1. Synthesis of (*S*)-14 from 4-Bromobenzaldehyde

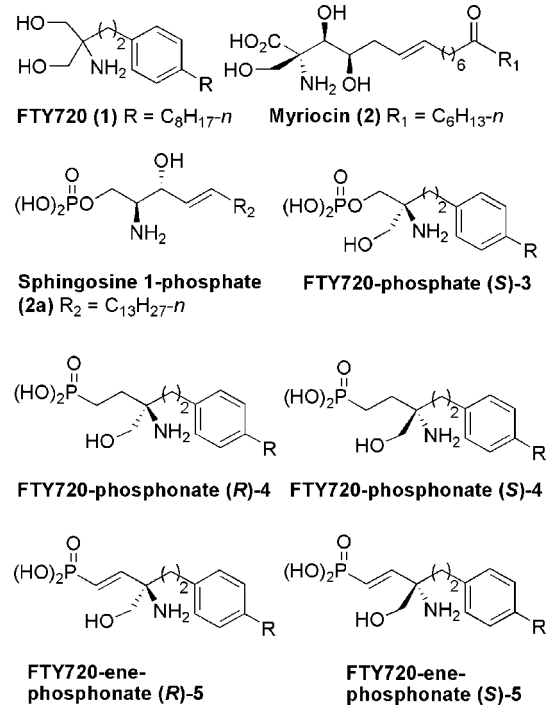


Eschenmoser's salt,[9] afforded α-methylene aldehyde **10**. Reduction of **10** with $NaBH_4$ in the presence of $CeCl_3$ (to suppress conjugate reduction) gave allyl alcohol **11**.[10] $CeCl_3$, which is a mild Lewis acid, is not required, since CsCl also provided **11** as the only product. Asymmetric Sharpless epoxidation[11] of **11** with cumene hydroperoxide (CHP) in the presence of L-(+)-DIPT, Ti(OPr-*i*)$_4$, and molecular sieves gave epoxide (*S*)-**12**.[12] The synthesis of (*S*)-**12** was accomplished in 7 steps from *p*-bromobenzaldehyde and in 46% overall yield. Reaction of alcohol (*S*)-**12** with trichloroacetonitrile in the presence of DBU gave 2,3-epoxy-1-trichloroacetimidate (*R*)-**13**. The tetrasubstituted carbon in oxazoline **14** was set up bearing the desired nitrogen substituent by opening of epoxide (*R*)-**13** with catalytic Et_2AlCl,[13] affording (*S*)-**14** in 74% yield for the two steps.

Swern oxidation of oxazoline (*S*)-**14** gave oxazoline aldehyde **15** (Scheme 2), which on Horner-Wadsworth-Emmons reaction with tetramethyl methylenediphosphonate afforded ester (*S*)-**16** in 87% yield and with an *E*/*Z* ratio of ∼10:1. Simultaneous demethylation and release of the hydroxy and amino groups by treatment with trimethylsilyl bromide (TMSBr) provided (*S*)-**5**, but the yield was low. Therefore, the hydroxy and amino groups were first released by treatment with 1 M HCl. After the amine hydrochloride was neutralized (saturated aq Na_2CO_3), amino alcohol **17** was converted to (*S*)-**5** with TMSBr followed by 95% methanol; 84% yield for the two steps. Reduction of (*S*)-**5** using Pearlman's catalyst gave (*S*)-**4**.

Asymmetric epoxidation of **11** with D-(-)-DIPT gave epoxide (*R*)-**12**, which was converted via (*R*)-**14** to (*R*)-**5** in six steps (Scheme 3). Catalytic hydrogenation of (*R*)-**5** afforded (*R*)-**4**.

CHART 1. Structures of FTY720 (1); Myriocin (2); S1P (2a); and FTY720 Phosphate, Phosphonate, and (*E*)-Vinylphosphonate Analogues (3−5)



S1P promotes the survival of many cell types.[14] Both **2a** and (*S*)-**3** protect oligodendrocyte progenitor cells from apoptotic cell death in response to growth factor withdrawal, and (*S*)-**3** was also shown to be cytoprotective in response to pro-apoptotic

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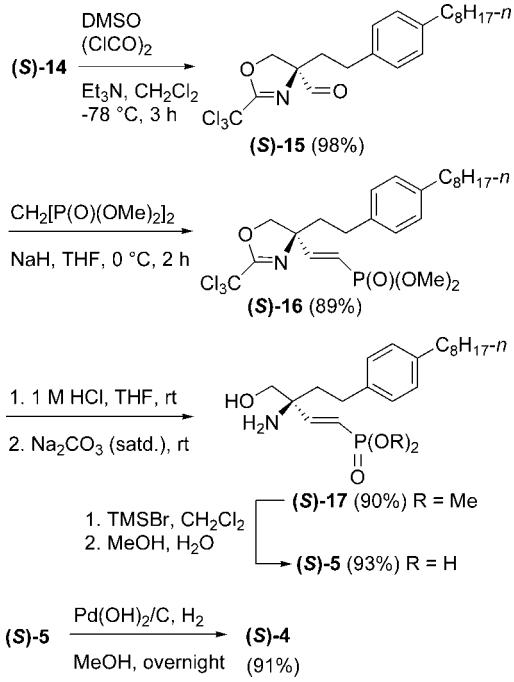
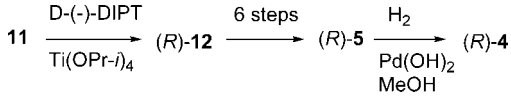
SCHEME 2. Synthesis of (*S*)-4 from (*S*)-14



SCHEME 3. Outline of the Synthesis of (*R*)-5 and (*R*)-4



cytokines and microglial activation.[15] The ability of **2a**, (*S*)-**3**, and phosphonate analogues **4** and **5** to protect IEC-6 cells from apoptotic cell death in response to the topoisomerase inhibitor CPT was assessed by DNA fragmentation. Pretreatment with **2a**, (*S*)-**3**, (*R*)-**4**, or (*R*)-**5** did not result in a significant reduction in DNA fragmentation in response to a 4-h treatment with 20 μM CPT. However, we found that the cytoprotective effect was enantioselective, since pretreatment with 1 μM of (*S*)-**4** or (*S*)-**5** showed a significant reduction (21 and 50%, respectively) in DNA fragmentation in response to CPT.

In a preliminary study of the activity of the FTY720-phosphonate analogues on S1P receptors, we performed Ca^{2+} mobilization assays with HTC4 cells that were stably transfected with $S1P_1$. As shown in Figure 1, the $S1P_1$ transfectants were activated by (*S*)-**3** to 76% of the maximal S1P-induced activation, and displayed a similar potency as S1P (13 $\pm$ 2 nM for S1P vs 9 $\pm$ 1 nM for (*S*)-**3**). (*R*)-**5** and (*R*)-**4** both showed a modest activity against $S1P_1$ with E_{max} values that ranged from 73 to 93% of the maximal S1P-induced responses, and EC_{50} values that were increased by ~2- to 3-fold. (*S*)-**4** activated $S1P_1$ to 36% of the maximal S1P-induced response, and the EC_{50} value was increased by ~5-fold to 75 $\pm$ 21 nM. Since (*S*)-**5** did not elicit a Ca^{2+} response from cells transfected with the $S1P_1$ receptor, we conclude that the potent cytoprotective effect of (*S*)-**5** is not mediated by $S1P_1$.

In conclusion, we have described the synthesis of the enantiomers of FTY720 phosphonate analogues **4** and **5**. (*S*)-**4** and (*S*)-**5**, but not **2a** or (*S*)-**3**, all at 1 μM, protected IEC-6 cells from apoptosis. The extent of CPT-induced DNA fragmentation was reduced by 50% and 21% in the presence of 1 μM of (*S*)-**5** and (*S*)-**4**, respectively. The potent cytoprotective activity of (*S*)-**5** is not mediated by $S1P_1$. Experiments are underway to characterize the cellular effects of these analogues.

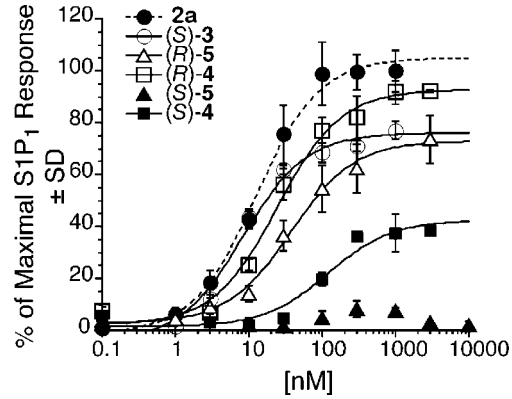


FIGURE 1. Ca^{2+} mobilization dose−response relationships for S1P (**2a**), (*S*)-**3**, and FTY720 analogues **4** and **5** in HTC4 cells expressing the $S1P_1$ receptor.

Experimental Section

(2*S*)-2-(2′-(Trichloromethyl)-4′,5′-dihydrooxazol-5-yl)-4-(4″-octylphenyl)-butan-1-ol [(*S*)-(+)-14]. To a solution of 435 mg (1.5 mmol) of epoxy alcohol (*S*)-**12** in 25 mL of CH_2Cl_2 at 0 °C were added Cl_3CCN (0.17 mL, 1.65 mmol) and DBU (0.023 mL, 0.15 mmol). After being stirred at 0 °C for 1.5 h, the reaction mixture was diluted with Et_2O (20 mL) and water (20 mL). The organic layer was separated, washed with brine (20 mL), dried ($MgSO_4$), and concentrated. The residue was purified by chromatography (hexane/EtOAc 20:1) to give 565 mg (87%) of (*R*)-**13**; R_f 0.58 (EtOAc/hexane 1:3). To an ice-cold solution of 565 mg (1.31 mmol) of (*R*)-**13** in 20 mL of CH_2Cl_2 was added Et_2AlCl (0.75 mL, 0.75 mmol, a 1.0 M solution in hexane). After the mixture was stirred at 0 °C for 20 min and then at rt for 3 h, the reaction was quenched with saturated aq $NaHCO_3$ solution (20 mL). The organic layer was washed with brine (20 mL), dried ($MgSO_4$), and concentrated. The residue was purified by chromatography (hexane/EtOAc 3:1) to give 480 mg (85%) of (*S*)-**14** as a white solid; mp 56.7−57.5 °C; R_f 0.29 (EtOAc/hexane 1:3); $[\alpha]^{25}_D$ +24.9 (*c* 1.60, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 6.8 Hz), 1.26−1.38 (m, 10H), 1.58 (m, 2H), 1.84 (m, 1H), 2.01 (m, 1H), 2.57 (m, 4H), 3.30 (s, 1H), 3.55 (dd, 1H, J = 11.6, 8.4 Hz), 3.85 (dd, 1H, J = 11.6, 4.8 Hz), 4.45 (d, 1H, J = 8.4 Hz), 4.65 (d, 1H, J = 8.4 Hz), 7.08 (s, 4H); ^{13}C NMR ($CDCl_3$) 14.2, 22.7, 29.3, 29.4, 29.5, 29.8, 31.6, 32.0, 35.6, 37.6, 66.8, 76.0, 86.5, 128.2, 128.9, 138.2, 140.8, 163.2. HRMS (MNa^+) *m/z* calcd for $C_{21}H_{30}Cl_3NO_2Na$ 456.1234, found 456.1241. Data for (*R*)-(**14**): $[\alpha]^{25}_D$ −25.0 (*c* 2.75, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 6.8 Hz), 1.26−1.38 (m, 10H), 1.58 (m, 2H), 1.85 (m, 1H), 2.01 (m, 1H), 2.14 (s, 1H), 2.60 (m, 4H), 3.54 (d, 1H, J = 11.6 Hz), 3.83 (d, 1H, J = 11.6 Hz), 4.45 (d, 1H, J = 8.4 Hz), 4.63 (d, 1H, J = 8.4 Hz), 7.09 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 29.0, 29.3, 29.5, 29.7, 31.6, 31.9, 35.5, 37.5, 67.0, 75.9, 86.4, 128.1, 128.6, 138.1, 140.9, 163.3.

(3*S*)-3-(Amino)-3-(hydroxymethyl)-5-(4′-octylphenyl)-pent-(1*E*)-enyl-phosphonic acid [(*S*)-(+)-5]. To a solution of 269 mg (0.50 mmol) of (*S*)-**16** in 10 mL of THF at rt was added 3 mL of 1 M HCl. After the reaction mixture was stirred overnight, the solvent was evaporated and the residue was extracted with a mixture of $CHCl_3$ and saturated Na_2CO_3 aq solution. The organic phase was dried ($MgSO_4$) and concentrated. The residue was purified by chromatography ($CHCl_3$/MeOH/NH_4OH 135:25:4) to give 185 mg (90%) of (*S*)−**17** as a pale yellow oil after filtration through a Teflon syringe filter. R_f 0.37 ($CHCl_3$/MeOH/NH_4OH 135:25:4); $[\alpha]^{25}_D$ +18.8 (*c* 1.52, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 6.4 Hz), 1.26−1.29 (m, 10H), 1.58 (m, 2H), 1.48−1.86 (m, 5H), 2.49−2.58 (m, 4H), 3.50 (dd, J = 21.2, 10.6 Hz), 3.73 (s, 3H), 3.75 (s,

3H), 5.93 (dd, 1H, J = 20.0, 17.6 Hz), 6.85 (dd, 1H, J = 22.8, 17.6 Hz), 7.05−7.10 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 29.3, 29.36, 29.44, 29.5, 31.6, 31.9, 35.5, 39.4, 52.4 (d, J = 6.0 Hz), 59.4 (d, J = 19.1 Hz), 69.2, 115.0 (d, J = 188.1 Hz), 128.1, 128.3, 128.6, 138.6, 140.8, 157.9 (d, J = 6.0 Hz); ^{31}P NMR ($CDCl_3$) δ 21.8. Data for (*R*)-(**17**): $[\alpha]^{25}_D$ −17.1 (c 1.51, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 6.4 Hz), 1.26−1.29 (m, 10H), 1.58 (m, 2H), 1.79−1.82 (m, 5H), 2.53−2.57 (m, 4H), 3.50 (dd, J = 21.2, 10.6 Hz), 3.73 (s, 3H), 3.75 (s, 3H), 5.93 (dd, 1H, J = 20.0, 17.6 Hz), 6.85 (dd, 1H, J = 22.8, 17.6 Hz), 7.07−7.10 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.7, 29.3, 29.4, 29.42, 29.5, 29.7, 31.6, 31.9, 35.5, 39.4, 52.4 (d, J = 2.0 Hz), 52.5 (d, J = 2.0 Hz), 59.4 (d, J = 19.1 Hz), 69.1, 115.0 (d, J = 188.1 Hz), 128.1, 128.4, 128.5, 138.7, 140.7, 157.9 (d, J = 6.0 Hz); ^{31}P NMR ($CDCl_3$) δ 21.8. To a solution of (*S*)-**17** in 10 mL of dry CH_2Cl_2 at rt was added 0.66 mL (5.0 mmol) of TMSBr. After the reaction mixture was stirred for 4 h, the solvent was removed, and the residue was dried and dissolved in 2 mL of 95% MeOH with stirring for 1 h. Removal of the solvent afforded 224 mg (93%) of (*S*)-**5** as a white solid: mp 159.2−161.1 °C; R_f 0.14 ($CHCl_3$/MeOH/H_2O/AcOH 65:25:4:1); $[\alpha]^{25}_D$ +12.2 (*c* 1.04, $CHCl_3$/MeOH 9:1); ^{1}H NMR ($CDCl_3$/CD_3OD 9:1) δ 0.87 (t, 3H, J = 6.8 Hz), 1.26 (br s, 10H), 1.51 (s, 2H), 1.95−2.10 (m, 2H), 2.47 (t, 2H, J = 7.6 Hz), 2.55−2.68 (m, 2H), 3.83 (br s, 2H), 4.08 (br s, 4H), 6.30 (m, 1H), 6.60 (m, 1H), 6.99 (d, 2H, J = 8.0 Hz), 7.07 (d, 2H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$/CD_3OD 9:1) δ 14.1, 22.9, 29.1, 29.5, 29.6, 31.8, 32.3, 35.8, 36.5, 62.2 (d, J = 20.1 Hz), 64.4, 123.3, 125.2, 128.3, 128.9, 137.6, 141.4, 144.2; ^{31}P NMR ($CDCl_3$/CD_3OD 9:1) δ 13.1. HRMS (MNa^+) *m*/*z* calcd for $C_{20}H_{34}NO_4PNa$ 406.2118, found 406.2106.

Data for (*R*)-5. $[\alpha]^{25}_D$ −13.0 (*c* 1.05, $CHCl_3$/MeOH 9:1); ^{1}H NMR ($CDCl_3$/CD_3OD 9:1) δ 0.88 (t, 3H, J = 6.8 Hz), 1.26−1.27 (m, 10H), 1.52−1.55 (m, 2H), 2.01−2.11 (m, 2H), 2.52 (t, 2H, J = 7.6 Hz), 2.55−2.68 (m, 2H), 3.26 (br s, 4H), 3.82 (br s, 2H), 6.30 (m, 1H), 6.59 (dd, 1H, J = 23.2, 18.0 Hz), 7.03 (d, 2H, J = 8.0 Hz), 7.08 (d, 2H, J = 8.0 Hz), 8.34 (br s, 1H); ^{13}C NMR ($CDCl_3$/CD_3OD 9:1) δ 14.2, 22.9, 29.0, 29.5, 29.6, 29.7, 29.9, 31.8, 32.3, 35.8, 36.5, 62.2 (d, J = 20.1 Hz), 64.4, 123.4, 125.2, 128.3, 128.9, 137.6, 141.4, 144.2; ^{31}P NMR ($CDCl_3$/CD_3OD 9:1) δ 13.1.

Acknowledgment. This work was supported by NIH Grants HL083187 and CA92160.

Supporting Information Available: Experimental details for the synthesis of compounds **6**−**8**, **10**, **11**, **12**, **16**, and **4**, and NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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